Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women

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Processed meat consumption has been associated with an increased risk of stomach cancer in some epidemiological studies (mainly case–control). Nitrosamines may be responsible for this association, but few studies have directly examined nitrosamine intake in relation to stomach cancer risk. We prospectively investigated the associations between intakes of processed meat, other meats and *N*-nitrosodimethylamine (the most frequently occurring nitrosamine in foods) with risk of stomach cancer among 61,433 women who were enrolled in the population-based Swedish Mammography Cohort. Information on diet was collected at baseline (between 1987 and 1990) and updated in 1997. During 18 years of follow-up, 156 incident cases of stomach cancer were ascertained. High consumption of processed meat, but not of other meats (*i.e.*, red meat, fish and poultry), was associated with a statistically significant increased risk of stomach cancer. After adjustment for potential confounders, the hazard ratios for the highest compared with the lowest category of intake were 1.66 (95% CI = 1.13–2.45) for all processed meats, 1.55 (95% CI = 1.00–2.41) for bacon or side pork, 1.50 (95% CI = 0.93–2.41) for sausage or hotdogs and 1.48 (95% CI= 0.99–2.22) for ham or salami. Stomach cancer risk was 2-fold higher among women in the top quintile of *N*-nitrosodimethylamine intake when compared with those in the bottom quintile (hazard ratio = 1.96; 95% CI = 1.08–3.58). Our findings suggest that high consumption of processed meat may increase the risk of stomach cancer. Dietary nitrosamines might be responsible for the positive association.
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Diet is a potentially modifiable exposure that is assumed to play a major role in the etiology of stomach cancer,[1] the second leading cause of cancer-related death worldwide.[2] Among dietary factors, high intake of processed meat, which includes meats preserved by salting, smoking or the addition of nitrites or nitrates, might be associated with elevated risk of stomach cancer. In 1997, the World Cancer Research Fund and the American Institute for Cancer Research[1] stated that diets high in processed meat may increase the risk of stomach cancer, but that the evidence was yet insufficient. However, that conclusion was based mainly on case–control studies, which are more susceptible to systematic bias than prospective cohort studies, and recent prospective studies have been inconsistent.[3–6]

Besides much salt and nitrites or nitrates, processed meat products like bacon, sausage and ham often contains carcinogenic nitrosamines.[7–9] *N*-nitrosodimethylamine (NDMA) is the most frequently occurring nitrosamine in foods.[10] Nitrosamines can also be formed endogenously in the stomach through nitrosation of nitrite with amines.[7] To date, 5 case–control studies[11–15] and only 1 prospective cohort study[3] with a small number of cases (*n* = 68) have investigated the association between NDMA or nitrosamine intake and stomach cancer risk, with 4 case–control studies[11–13,15] showing a positive association.

To examine whether associations exist between intake of processed meat and NDMA and risk of stomach cancer, we used prospective data from the Swedish Mammography Cohort, a large population-based cohort with 18 years of follow-up and repeated assessments of diet. In addition, we evaluated risk of stomach cancer in relation to consumption of red meat, poultry and fish.

Material and methods

Study population

The Swedish Mammography Cohort is a population-based prospective cohort study established between 1987 and 1990, when all women born between 1914 and 1948 and residing in Uppsala and Västmanland counties in central Sweden received a mailed questionnaire on diet, alcoholic beverages, weight, height and education. Of the 90,303 women in the source population, 66,651 (74%) returned a completed questionnaire. In the autumn of 1997, a second questionnaire was sent to all women who were still alive and residing in the study area to update information on diet and to collect data on other lifestyle factors (including cigarette smoking); 39,227 women (70% response rate) answered the questionnaire.

For the analyses presented here, we excluded from the baseline population women with erroneous or missing national registration number; those who reported implausible values for total energy intake (*i.e.*, 3 standard deviations from the mean value of log-transformed energy intake); and those with a previous cancer diagnosis (except nonmelanoma skin cancer). These exclusions left a total of 61,433 women for the analyses. The investigation was approved by the Regional Ethical Review Board in Stockholm.

Dietary assessment

At baseline, a 67-item food-frequency questionnaire (FFQ) was used to assess dietary intake. An expanded 96-item FFQ was used to update information on dietary intake in 1997. In these FFQs, women reported their average frequency of consumption of each food item over the past year. We considered processed meat to include the following grouped items on the FFQ: bacon or side pork, sausage or hotdogs, and ham or salami. Red meat (unprocessed) was considered to include minced meat (hamburgers, meatballs, meatloaf, *etc.*); casserole with beef, pork, or veal; and whole beef (steaks, roasts, *etc.*). Poultry consisted of chicken, hens and other poultry. Fish included lean fish (cod etc), fatty fish (salmon, herring, sardines, mackerel, *etc.*) and tuna. To calculate amounts of foods consumed, we used age-specific portion sizes for foods that were based on mean values obtained from 213 randomly selected women from the study area who weighed and recorded their food intake for 27.8 days on average (A. Wolk, unpublished data). The mean daily food consumption (g/day) was calculated by multiplying consumption frequency and age-specific portion size.

We calculated NDMA intake by multiplying the average frequency of consumption of each food item by the NDMA content of age-specific portion sizes. Values for NDMA in foods were obtained from tables compiled by Österdahl based on foods on the

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Swedish market in 1980–1988.[10,16,17] Foods included in the calculation of NDMA intake were specific processed meat products (bacon, side pork, sausages, ham), smoked fish, caviar and roe, alcoholic beverages (light beer, medium-strong beer, strong beer, whiskey) and chocolate.

The baseline FFQ has been validated in a subsample of 129 women randomly chosen from the study population. The Spearman correlation coefficients between the FFQ and the average of four 1-week weighted diet records ranged from 0.3 to 0.7 for processed and red meat items and from 0.4 to 0.5 for fish items; the correlation coefficient was 0.4 for poultry (A. Wolk, unpublished data, 1992).

Ascertainment of cases and follow-up

Incident cases of stomach cancer (*International Classification of Diseases*, 9th Revision code 151) were ascertained through computerized linkage of the study population with the national and regional Swedish Cancer registers. These registers have been estimated to provide close to 100% complete case ascertainment in Sweden.[18,19] From the Swedish Death and Population registers at Statistics Sweden, we obtained information on dates of death and migration, when applicable.

Statistical analysis

Person-time was accrued for each participant from the date of entry into the cohort to the date of diagnosis of stomach cancer, death, migration, or December 31, 2004, whichever came first. We categorized participant into approximate tertiles according to intake of processed meat, red meat, poultry and fish, and into quintiles according to NDMA intake. To better represent long-term average intake and to reduce random within-person variation, stomach cancer incidence was related to the cumulative average intake at baseline and in 1997. Specifically, the baseline intake was used for the 1987–1997 follow-up period, and the average of the baseline and 1997 intake was used for 1998–2004 follow-up.

We used Cox proportional hazards models[20] (PROC PHREG in SAS version 9.1 software; SAS Institute, Cary, NC) to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Age in months and year of entry into the cohort was used as stratification variables in the Cox model. In all multivariate analyses, we controlled for age, education (less than high school, high school graduate, or more than high school), body mass index (the weight in kilograms divided by the square of height in meters; <23.0, 23.0–24.9, 25.0–29.9, or ≥30) and intakes of total energy (continuous), alcohol (quartiles), fruits (quartiles) and vegetables (quartiles). Cox proportional hazards assumption was tested for meat, poultry, fish and NDMA intake variables in relation to risk of stomach cancer using the likelihood ratio test; there was no violation of the proportional hazards assumption.

To test for linear trend across categories, we modeled meat, fish, poultry and NDMA intake as single continuous variables using the median value within categories. We conducted analyses of processed meat and NDMA intake stratified by intake of vitamins C and E, and fruit and vegetables to evaluate whether the association of processed meat or NDMA intake with risk of stomach cancer was modified by these dietary factors. Tests for interaction were performed by using the median value for each category of processed meat or NDMA intake to form a continuous variable, an indicator variable (using the median intake as a cutoff point) for vitamin C (<75 mg/day *vs.* ≥75 mg/day), vitamin E (<5.7 mg/day *vs.* ≥5.7 mg/day), or fruit and vegetables (<3 servings per day *vs.* ≥3 servings per day), and an interaction term for the product of 2 variables. We used the Wald test to assess the statistical significance of the multiplicative interaction term. All *p*-values are 2-tailed.

Results

At baseline, there was an almost 5-fold difference in the median consumption of processed meat between the highest and the low-

TABLE I – AGE-STANDARDIZED BASELINE CHARACTERISTICS BY PROCESSED MEAT CONSUMPTION

Characteristic	Processed meat intake (servings per week)		
	<1.5 $(0.9)^1$	1.5–2.9 (2.1)	≥3.0 (4.2)
Age (years)	54.7	52.2	53.3
Body mass index (kg/m^2)	24.5	24.8	25.0
Post-secondary education (%)	14.1	11.2	11.6
Ever smoker (%)^2	47.5	46.3	44.4
Mean daily intake			
Total energy (kcal)	1,453	1,593	1,757
Alcohol (g)	3.1	3.0	3.1
Fruits (servings)	1.8	1.7	1.7
Vegetables (servings)	1.8	1.6	1.7

^{1}Values in parentheses are medians.–^{2}Information from the 1997 questionnaire.

est categories (Table I). Women with a higher processed meat consumption were younger, had a higher body mass index, and were slightly less likely to have a postsecondary education when compared with those with a low processed meat consumption. Cigarette smoking and intake of alcohol, fruits and vegetables were not appreciably associated with processed meat consumption.

Among the 61,433 eligible women, we ascertained 156 incident cases of stomach cancer during 940,770 person-years of follow-up from 1987 through 2004. Increasing consumption of processed meat was statistically significantly associated with increasing risk of stomach cancer (Table II). In an age-adjusted analysis, the HR for women in the highest category of processed meat consumption was 1.69 (95% CI = 1.17–2.45; *p*-trend = 0.008) when compared with those in the lowest category. The association remained essentially unchanged after additional adjustment for other potential confounders (HR = 1.66; 95% CI = 1.13–2.45; *p*-trend = 0.01). All individual processed meat items examined were positively associated with stomach cancer risk (Table II). The multivariate HRs comparing the highest with the lowest category of intake were 1.55 (95% CI = 1.00–2.41) for bacon or side pork, 1.50 (95% CI = 0.93–2.41) for sausage or hotdogs and 1.48 (95% CI = 0.99–2.22) for ham or salami.

To evaluate the possibility that preclinical symptoms of stomach cancer caused a change in diet, thereby biasing our results, we conducted an analysis excluding cases that were diagnosed during the first 3 years of follow-up. The positive association of processed meat consumption with stomach cancer risk became stronger. The multivariate HR for the highest compared with the lowest category of processed meat consumption was 1.78 (95% CI = 1.15–2.75; *p*-trend = 0.01).

Information on cigarette smoking was collected first in the second questionnaire. In a subanalysis of women who completed this questionnaire and with follow-up from 1998 through 2004 (including 52 incident cases), we assessed whether adjustment for smoking (never, past or current smoker) altered our results for processed meat consumption. The results were identical in multivariate analyses that adjusted for the covariates listed in Table II and in analyses further controlled for smoking (HR = 1.65; 95% CI = 0.80–3.39 for highest *vs.* lowest category).

The associations between consumption of red meat (beef, pork, lamb or veal), poultry and fish with stomach cancer are presented in Table III. High poultry consumption was associated with a statistically nonsignificant decreased risk (multivariate HR = 0.58; 95% CI = 0.31–1.09, for highest *vs.* lowest category). This association persisted after adjustment for processed meat consumption (HR = 0.57; 95% CI = 0.31–1.08). Similarly, the observed positive association between processed meat consumption and stomach cancer risk remained after controlling for poultry consumption (multivariate HR = 1.67; 95% CI = 1.13–2.47, for ≥3 servings per day *vs.* <1.5 serving per day of

TABLE II – HAZARD RATIOS OF STOMACH CANCER BY PROCESSED MEAT CONSUMPTION

Food item	Category of intake			p-trend
	1 (lowest)	2	3 (highest)	
Processed meat				
Servings per week	<1.5	1.5–2.9	≥3.0	
No. of cases	51	38	67	
Person-years of follow-up	389,577	228,549	322,644	
Age-adjusted HR (95% CI)	1.00	1.49 (0.97–2.28)	1.69 (1.17–2.45)	0.008
Multivariate HR (95% CI)[1]	1.00	1.46 (0.95–2.25)	1.66 (1.13–2.45)	0.01
Bacon or side pork				
Servings per week	0	0.1–0.4	≥0.5	
No. of cases	52	66	38	
Person-years of follow-up	368,258	410,388	162,124	
Age-adjusted HR (95% CI)	1.00	1.28 (0.89–1.85)	1.58 (1.04–2.42)	0.03
Multivariate HR (95% CI)[1]	1.00	1.27 (0.88–1.85)	1.55 (1.00–2.41)	0.05
Sausage or hot dogs				
Servings per week	<0.4	0.4–0.9	≥1.0	
No. of cases	24	55	77	
Person-years of follow-up	166,070	303,817	470,883	
Age-adjusted HR (95% CI)	1.00	1.42 (0.88–2.31)	1.52 (0.96–2.42)	0.10
Multivariate HR (95% CI)[1]	1.00	1.44 (0.89–2.35)	1.50 (0.93–2.41)	0.13
Ham or salami				
Servings per week	<0.4	0.4–1.4	≥1.5	
No. of cases	45	46	65	
Person-years of follow-up	282,355	373,041	285,374	
Age-adjusted HR (95% CI)	1.00	0.97 (0.64–1.47)	1.51 (1.03–2.23)	0.01
Multivariate HR (95% CI)[1]	1.00	0.97 (0.65–1.51)	1.48 (0.99–2.22)	0.03

[1]Adjusted for age (in months), education (less than high school, high school graduate, or more than high school), body mass index (<23.0, 23.0–24.9, 25.0–29.9, or ≥30 kg/m^2), and intakes of total energy (continuous), alcohol (quartiles), fruits (quartiles), and vegetables (quartiles).

TABLE III – TABLE–HAZARD RATIOS OF STOMACH CANCER BY RED MEAT, POULTRY AND FISH CONSUMPTION

Food item	Category of intake			p-trend
	1 (lowest)	2	3 (highest)	
Red meat[1]				
Servings per week	<2.0	2.0–3.4	≥3.5	
No. of cases	56	60	40	
Person-years of follow-up	298,179	374,126	268,465	
Age-adjusted HR (95% CI)	1.00	1.10 (0.76–1.60)	1.14 (0.75–1.74)	0.53
Multivariate HR (95% CI)[2]	1.00	1.07 (0.73–1.57)	1.07 (0.69–1.66)	0.76
Poultry				
Servings per week	<0.2	0.2–0.4	≥0.5	
No. of cases	61	82	13	
Person-years of follow-up	280,957	530,691	129,122	
Age-adjusted HR (95% CI)	1.00	0.91 (0.65–1.28)	0.63 (0.34–1.15)	0.17
Multivariate HR (95% CI)[2]	1.00	0.89 (0.63–1.26)	0.58 (0.31–1.09)	0.12
Fish				
Servings per week	<1.2	1.2–1.9	≥2.0	
No. of cases	50	50	56	
Person-years of follow-up	311,479	350,108	279,183	
Age-adjusted HR (95% CI)	1.00	1.00 (0.67–1.49)	1.20 (0.81–1.77)	0.31
Multivariate HR (95% CI)[2]	1.00	0.97 (0.64–1.46)	1.14 (0.75–1.72)	0.53

[1]Red meat indicates beef, pork, lamb or veal as a main dish.–[2]Adjusted for age (in months), education (less than high school, high school graduate or more than high school), body mass index (<23.0, 23.0–24.9, 25.0–29.9 or ≥30 kg/m^2) and intakes of total energy (continuous), alcohol (quartiles), fruits (quartiles) and vegetables (quartiles).

processed meat). There were no associations for red meat or fish consumption.

When analyzed as continuous variables, the multivariate HRs for an increment of 10 g per day in intake were 1.16 (95% CI = 1.00–1.35) for processed meat, 1.02 (95% CI = 0.96–1.08) for red meat, 0.79 (95% CI = 0.60–1.05) for poultry and 1.03 (95% CI = 0.95–1.11) for fish.

We next examined the association between dietary NDMA intake and stomach cancer risk. There was a statistically significant positive trend of increasing risk of stomach cancer across quintiles of NDMA intake (Table IV). Compared with women in the lowest quintile of NDMA intake, those in the fifth quintile had a 2-fold elevated risk of stomach cancer (multivariate HR = 1.96; 95% CI = 1.08–3.58).

Because vitamins C and E, polyphenols, and fruit and vegetable juices have been shown to inhibit the formation of N-nitroso compounds in the stomach,[21] we investigated whether the association of processed meat or NDMA intake with risk of stomach cancer was modified by intake of vitamins C or E, or fruit and vegetables. The association with processed meat intake was slightly stronger among women with low (<3 servings per day) fruit and vegetable consumption (HR = 1.97; 95% CI = 1.12–3.44, for highest vs. lowest intake category) than among those with high (≥3 servings per day) fruit and vegetable consumption (HR = 1.41; 95% CI = 0.81–2.48), but a test for interaction was not statistically significant (p-interaction = 0.15). Likewise, the relation with NDMA intake was stronger among women with low fruit and vegetable consumption (HR = 3.00; 95% CI = 1.25–7.17, for

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TABLE IV – HAZARD RATIOS OF STOMACH CANCER BY *N*-NITROSODIMETHYLAMINE (NDMA) INTAKE

	Quintile of NDMA intake, μg/day					*p*-trend
	<0.041	0.041–0.078	0.079–0.120	0.121–0.193	≥0.194	
Median intake	0.017	0.061	0.098	0.151	0.277	
No. of cases	28	28	37	32	31	
Person-years of follow-up	190,011	190,002	185,879	186,639	188,238	
Age-adjusted HR (95% CI)	1.00	1.03 (0.60–1.75)	1.62 (0.99–2.68)	1.51 (0.90–2.53)	1.81 (1.07–3.07)	0.01
Multivariate HR (95% CI)[1]	1.00	1.03 (0.61–1.77)	1.66 (1.00–2.75)	1.60 (0.93–2.76)	1.96 (1.08–3.58)	0.02

[1]Adjusted for age (in months), education (less than high school, high school graduate or more than high school), body mass index (<23.0, 23.0–24.9, 25.0–29.9 or ≥30 kg/m^2) and intakes of total energy (continuous), alcohol (quartiles), fruits (quartiles) and vegetables (quartiles).

highest *vs.* lowest intake category) than among those with high fruit and vegetable consumption (HR = 1.31; 95% CI = 0.53–3.22); *p*-interaction = 0.06. The association of processed meat or NDMA intake with stomach cancer did not appear to differ according to level of vitamin C or vitamin E intake (*p*-interaction > 0.55 for all).

Discussion

In this large population-based prospective study, we found that high consumption of processed meat was associated with a significant increased risk of stomach cancer. Furthermore, women in the highest quintile of dietary NDMA intake had a 2-fold higher risk when compared with those in the lowest quintile. Poultry consumption was associated with a nonsignificant decreased risk of stomach cancer, whereas no associations were observed for red meat or fish consumption.

Results from previous epidemiologic studies on processed meat consumption and stomach cancer risk have been inconsistent. Among case–control studies, 5 studies[22–26] have found a 2- to 3-fold statistically significant increase in stomach cancer risk associated with high consumption of processed meat, 6 studies[27–32] have observed a 30–70% increased risk but the results were not statistically significant, and 2 studies did not support an association.[33,34] In some case–control studies, positive associations were found for specific processed meat items, including bacon,[35,36] sausage[35,37,38] or ham.[35,39] The evidence from prospective cohort studies is less supportive of an association between processed meat consumption and risk of stomach cancer. In a cohort study in Japan,[4] processed meat consumption was associated with a statistically significant 2.7-fold elevated risk (excluding the first 2 years of follow-up). High processed meat consumption was associated with a nonsignificant 30% increased risk of stomach cancer in a cohort study in the United States.[40] However, 3 other cohort studies among American,[5] Japanese,[6] and Finnish populations[3] did not observe a positive relation with processed meat consumption. Two cohort studies, in the U.S.[41] and the Netherlands,[42] showed increases in stomach cancer risk with bacon consumption, and 1 Japanese cohort[43] found a positive association with sausage consumption. All previous prospective studies were based on a single assessment of diet, which could lead to misclassification of long-term average processed meat consumption and attenuate a potential association.

Processed meat is the major dietary source of volatile nitrosamines, contributing to about 80% of total intake in the Swedish diet.[10] Nitrosamines are potent carcinogens that can induce tumors in various animal species at a variety of sites.[7,9] Sugimura and Fujimura[44] demonstrated that gastric carcinomas were induced in rats in response to oral administration of a *N*-nitroso compound, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG). Results from our study suggest that nitrosamines might also play a role in the development of stomach cancer in humans. This finding is consistent with those from 4 case–control studies, in which a 1.4- to 7-fold increase in stomach cancer risk was found for high intake of NDMA or nitrosamines.[11–13,15] Another case–control study[14] and 1 small Finnish cohort study[3] of 9,985 individuals (including 68 cases) did not observe a positive association for NDMA intake.

In addition to nitrosamines, processed meat often contains much salt. Although salt is not intrinsically carcinogenic, diets high in salt could directly damage the gastric mucosa, leading to gastritis, increased DNA synthesis and cell proliferation.[45–47] In experimental studies with rats, salt enhances the carcinogenic effects of gastric carcinogens, such as MNNG.[48–50] Several case–control and ecological studies[1] and some prospective investigations[41,51] have suggested that high intakes of salt and salted foods may increase the risk of stomach cancer. Bacon and sausage, for which we observed positive associations with stomach cancer risk, also contains heterocyclic amines (HCAs) upon cooking at high temperatures.[52] HCAs are known mutagens and animal carcinogens.[52] Pence *et al.* showed that feeding of a diet high in HCAs resulted in increased stomach tumors in carcinogen-treated rats.[53] In our cohort, information on cooking methods and doneness preferences was not collected at baseline, and therefore we could not examine cooking practices and doneness preferences in the current study.

The main strengths of our study include its population-based and prospective design, the availability of dietary exposure information collected from participants at 2 time points and the practically complete follow-up of the study population through linkage with computerized registers. The prospective study design precluded potentially biased recall of dietary intake and the completeness of follow-up of the cohort minimized the concern that our findings have been affected by differential loss to follow-up. By using repeated measures of diet, we could obtain a better estimate of long-term meat and NDMA intake and reduce measurement error.

Our study also has several limitations. Because diet was assessed with a self-administered food-frequency questionnaire, some misclassification of meat and NDMA intake is inevitable, and random misclassification would tend attenuate any true relationship. Another potential limitation is an inability to examine risk by subsite and by histological subtype of stomach cancer, or by *Helicobacter pylori* infection status. Information on cigarette smoking was first obtained in the second questionnaire. Nevertheless, in a subanalysis using data from this questionnaire, the association between processed meat consumption and stomach cancer risk persisted after adjustment for smoking. Moreover, women with high consumption of processed meat were slightly less likely to smoke; thus, any residual confounding from smoking would be expected to attenuate the association. Finally, because of the observational nature of our study, we cannot rule out the possibility that an unevaluated risk factor for stomach cancer and that is correlated with processed meat consumption have had some effects on our results.

In conclusion, findings from this prospective study suggest that consumption of processed meat, but not of other meats, is positively associated with risk of stomach cancer. Nitrosamines in processed meat might be responsible for the association. Further research on processed meat consumption and, especially, on nitrosamines in relation to stomach cancer risk is warranted.

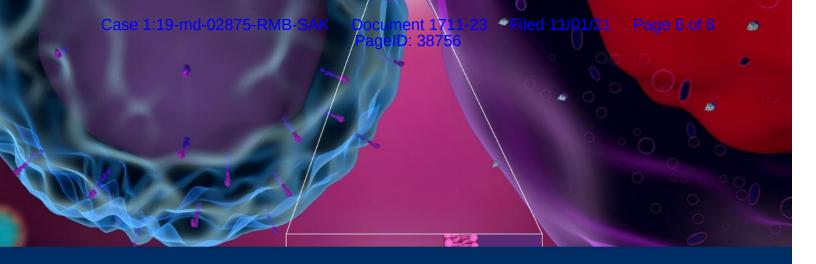PROCESSED MEAT CONSUMPTION, DIETARY NITROSAMINES AND STOMACH CANCER RISK   919

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